American Journal of Hematology 60:24–26 (1999)

Deferoxamine Treatment During Pregnancy: Is it Harmful?

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The use of the iron chelator, Deferoxamine (DFO), in pregnant thalassemia women with iron overload has been generally avoided due to fear of its potential teratogenicity. We describe a case of a pregnant thalassemia major patient with iron overload, who received DFO throughout her second and third trimesters and gave birth to a healthy infant, who had no findings of DFO toxicity at birth and at a later follow-up. Review of the literature discloses over 40 other cases in which DFO was given in various periods of gestation without evidence of teratogenic effect. Sufficient documentation exists, therefore, to suggest that DFO can be considered for use in cases of pregnant women who need iron chelation treatment. Am. J. Hematol. 60:24–26, 1999. © 1999 Wiley-Liss, Inc.

Key words: thalassemia; iron chelation; deferoxamine

INTRODUCTION

Improved pediatric and hematologic management has resulted in the survival of beta thalassemia major patients into adulthood. Consequently, the attention to reproductive potential has increased as well as the patients' desire to have a family. Recent reports have shown that a successful pregnancy is possible in women who are well chelated or who undergo ovulation induction [1,2].

It is well established that the transfusion requirement is increased throughout the pregnancy of thalassemia major patients. This allows proper fetal development and a full-term pregnancy [1–4]. However, no strategy for the management of the iron overload during gestation has been developed to date. The increased transfusion support results in further iron accumulation in patients who generally have a preexisting iron overload status, and therefore, it seems rather pressing to define the proper use of chelation treatment during pregnancy.

Deferoxamine (DFO), an effective iron chelator and the agent most commonly used in patients with thalassemia, has potential side effects, but it is uncertain whether it is teratogenic. Reports on patients receiving DFO during pregnancy are mostly anecdotal and reflect conflicting approaches as far as its safety for the developing fetus.

We report a case of a transfusion-dependent thalassemia major patient who was treated with DFO during her second and third trimesters and gave birth to a healthy baby without evidence of teratogenesis. We also review the literature on the use of DFO during pregnancy.

CASE REPORT

The patient is a 20-year-old female with hemoglobin E beta zero thalassemia, chronic hepatitis C, and iron overload. Her sister, who also had hemoglobin E beta zero thalassemia, died from iron overload complications at the age of 27. Starting at the age of six, when she arrived in the USA, the patient was transfused monthly to maintain her hemoglobin nadir above 9–10 g/dL. Chelation therapy with DFO was started at age eight and consisted of ~40 mg/kg four days a week, administered subcutaneously (SQ). An additional 50 mg/kg was given intravenously (IV) with her monthly transfusion. She was noncompliant at times and, at the age of sixteen, her ferritin levels ranged from 4,000 to 5,000 ng/ml, and her liver iron was 22 μg iron per gram of dry weight liver.

Contract grant sponsor: Maternal and Child Health Bureau (Title V, Social Security Act), Health Resources and Services Administration, Department of Health and Human Services; Contract grant number: MCJ-061016-06.

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Received for publication 16 July 1998; Accepted 12 August 1998

At the age of eighteen-and-a-half, she had a spontaneous intrauterine pregnancy. She then discontinued the use of DFO. At 16 weeks of gestation, her ferritin level was at 6,000 ng/ml, and the frequency of her blood transfusions had to be increased to maintain a hemoglobin nadir of 10 g/dL. A concern regarding the increased iron accumulation led to a medical decision and the patient's consent to resume DFO treatment. DFO was restarted at 18 weeks of gestation both as a SQ infusion of 40 mg/kg four days a week and IV treatment of 50 mg/kg every two weeks. At 26 weeks of gestation, her ferritin level was at 7,000 ng/ml, and the DFO dose was increased to 50 mg/kg/day and the IV dose to 80 mg/kg. Due to persistent elevation of her ferritin level at 30 weeks of gestation, DFO IV administration of ~50 mg/kg/day through a mediport was started. Her ferritin level between 30 and 38 weeks of gestation dropped to the 4,000–6,000 ng/dL range.

Overall, her pregnancy course was uncomplicated, except she had suboptimal weight gain during her third trimester and a central line sepsis event, which responded well to antibiotics. Fetal growth was appropriate as determined by ultrasound examinations. At 38 weeks of gestation, she gave birth to a normal baby boy who weighed 5 lbs. and 1 oz. Her blood requirement during 38 weeks of pregnancy was ~170 cc/kg (= ~250 cc/kg/year).

Follow-up of the child at the age of 10 months showed an age-appropriate developed boy. A comprehensive evaluation for potential DFO toxicity revealed a normal audiogram, a normal skeletal survey without evidence of bone dysplasia, and a normal ophthalmology exam without retinal changes.

DISCUSSION

Regular use of DFO has been shown to be effective in removing excess iron in patients on chronic transfusion and therefore preventing or delaying iron-induced organ damage. However, due to uncertainty of its safety for the developing fetus, it has generally been withheld during pregnancy [1,3–6]. Because of the concern over its teratogenic potential, the importance of contraception or preconceptual counseling has been addressed [1]. Others who shared the same concern developed programs aimed to prevent pregnancy among patients treated with iron chelators [7]. Two cases of abortions due to early exposure to DFO have been reported [1], and it is possible that other unreported cases had terminated pregnancies for the same reason.

Despite this general caution in using DFO during pregnancy, review of the literature on pregnant thalassemia women discloses over 40 patients who have received DFO during several weeks or months of gestation, and there is no single documentation of a toxic or teratogenic effect. A total of 11 cases in the various reports have continued the use of DFO in early pregnancy, most of them inadvertantly: four patients up to eight weeks [2,4]; five women up to 16 to 19 weeks of gestation [3,8–10]; and two women up to 21 and 26 weeks [1,10]. All gave birth to normal-appearing infants. Three of the infants were born premature at 32 and 33 weeks of gestation [3,8]. In another study, DFO was administered to 32 pregnant women with beta thalassemia major during the second and third trimesters and withheld during the first trimester. All had normal, term infants. No information is provided regarding the dose of DFO administered, but the authors state that ferritin levels remained overall stable despite the increased transfusion requirement [2]. Our case demonstrates another successful pregnancy with use of DFO in increasing doses (SQ and IV) during the second and third trimesters. It is the first reported case in which a follow-up examination of the child was obtained and no toxic effects of DFO on bone formation, auditory, or ocular systems were found.

A study of 25 pregnant women treated with DFO [11] and other case reports of iron intoxication [12–14] have also failed to show evidence of DFO toxicity to either the mother or the baby.

As new drugs are almost never tested in pregnant women, the potential teratogenicity of DFO in humans is based on animal studies. Experiments in pregnant mice have shown effects on bone formation only when large doses, up to five times the maximum daily human dose, were administered. Maternal toxicity, with all doses administered, consisted of lowered food consumption and lower body weight [15]. The manufacturer product information states similar results in rabbits as well as another study which showed no adverse effects in studies done in rats. However, despite this data on animals, none of the above reported cases in humans showed evidence for a similar DFO toxic effect. A recent review on drugs in pregnancy points out that although studies in animals may identify teratogenic effects, it can be difficult to extrapolate these effects to humans [16]. This could apply to the studies done with DFO. Furthermore, there is some doubt that DFO can cross the placenta due to its large molecular size and charge [17].

Eliminating the use of DFO during pregnancy could worsen tissue iron accumulation and aggravate iron-induced organ damage. If not adequately chelated, women with preexisting cardiac hemosiderosis may experience cardiovascular complications due to the changes of increased cardiac output and blood volume that occur during pregnancy. Therefore, this data suggests that, in a subgroup of women, the benefits to the mother outweigh the potential risks to the fetus, and DFO should not be withheld.

In general, unnecessary fetal exposure to drugs should be avoided. However, this case report and the review of

the literature suggest that, in cases of pregnancy in which DFO administration is considered, it is most likely safe. Further studies in humans looking at the pharmacokinetics of DFO, at levels of other metals which could potentially be chelated by this agent, and at the documentation of its use during pregnancy, are needed. This will help establish its safety, proper use for pregnant women, and the type of monitoring required.

ACKNOWLEDGMENTS

The authors acknowledge Alicia Easley, M.D., Dru Foote, P.N.P., and Keith Quirolo, M.D., for their technical support. This work was supported by the Northern California Thalassemia Center, a program of the Maternal and Child Health Bureau (Title V, Social Security Act), Health Resources and Services Administration, Department of Health and Human Services, MCJ-061016-06.

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